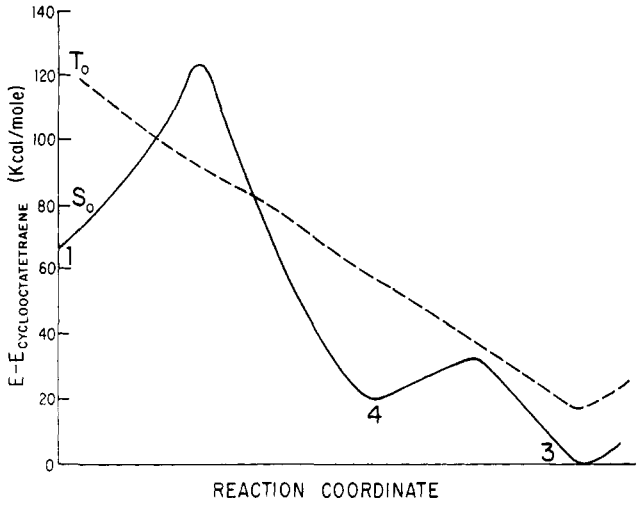
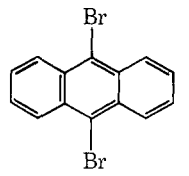


Figure 1. Cross section of S_0 and T_0 potential energy surfaces for the interconversion of **1** to **4.**

state of cyclooctatetraene; this is predicted to be planar, with D_{8h} symmetry, lying 17.8 kcal/mol above the ground state (C–C bond length, 1.403 Å). There may be a small subsidiary minimum corresponding to **4;** if so, however, the barrier separating it from triplet **3** is very low.

According to these results there are direct low energy paths from **1** or **2** to **3** *via* triplet intermediates, the initial product in each case being the triplet excited form of **3.** (Intermediate deactivation might lead to **4** but this would rearrange rapidly to **3** under the conditions of the reaction). The corresponding activation energies are: **1** → **3***, 36.0 kcal/mol; **2** → **3***, 39.3 kcal/mol. The agreement with experiment is quite close and the difference between the two values (3.3 kcal/mol) is essentially identical with that observed (3.6 kcal/mol).

These results therefore seemed to suggest rather strongly that the conversions of **1** or **2** to **3** must involve intersystem crossing as an integral part of the reaction, as apparently does the thermolysis of dioxetanes. If so, **3** should be formed initially in its triplet state. Unfortunately the triplet state of **3** lies so close to the ground state that its detection would be very difficult; we therefore looked for analogous processes that might be expected to take place in a similar way and lead to products with a greater singlet-triplet separation. Such high energy triplets can be detected by adding to the reaction mixture agents which can be excited by energy transfer and will then emit light, *e.g.,* 9,10-dibromoanthracene (**5**).[8]



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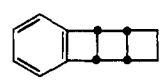

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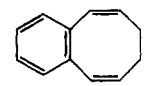

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An obvious choice seemed to be the *syn*-benzotricyclooctene (**6**) which can be made easily by reduction of the double bond in the codimer of cyclobutadiene and benzocyclobutadiene[9] and which is converted quantitatively on heating to benzo[*c*]-1,3,5-cyclooctatriene (**7**). In repeated experiments where solutions of **6** and **5** in decalin (30 mg and 100 mg per ml, respectively) were heated to temperatures over the range 150–200°, visible light was emitted corresponding to fluorescence from **5.** No light was emitted in control experiments when **6** was omitted and light emission died away with the disappearance of **6** (the lifetime of which could of course be estimated from the Arrhenius parameters). While the chemiluminescence was weak, Professor Turro (who is now examining the reaction in detail) has pointed out that the fluorescent efficiency of **5** at these temperatures is very low indeed so that the yield of triplet **7** must be quite high. There seems to be no case on record where a thermal reaction of a hydrocarbon has led with high efficiency to a triplet excited product.

This work reported here and in the two previous communications[7,10] therefore leads to the quite unexpected conclusion that apparently "normal" reactions may take place by mechanisms involving intersystem crossing and so lead to products in triplet excited states. The kinetic data moreover indicate that such reactions can occur with normal frequency factors. If these conclusions can be substantiated, they will open a Pandora's box of hitherto unexpected new chemiluminescent processes and a complete rethinking of ideas concerning the possible role of triplet states in thermal reactions.

References and Notes

(1) This work was supported by the Robert A. Welch Foundation through Grants No. F-067 and F-126, by the Air Force Office of Scientific Research through Contract No. F44620-71-C-0119, and by the National Science Foundation. The calculations were carried out using the CDC 6400/6600 computer at The University of Texas Computation Center.
(2) MINDO/3 is an improved version of the MINDO/2 semiempirical SCF MO method; R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Amer. Chem. Soc.,* in press.
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Received June 20, 1974

Total Synthesis of β-Lactam Antibiotics. VII.[1] Total Synthesis of (±)-1-Oxacephalothin

Sir:

Aside from the nitrogen atom, the cephalosporin and penicillin nuclei have sulfur as the only other heteroatom. Since the sulfur atom could possibly bind to an electrophilic site on the enzyme with which these molecules interact, it was of interest to determine whether sulfur is necessary for the biological activity of these compounds. Substitution of sulfur in the bicyclic system by a smaller atom could also result in higher strain in the system and, hence, a more reactive β-lactam moiety and therefore perhaps an antibiotic with increased activity.

Following the total syntheses of cephalothin (**13**) and cefoxitin (**14**) from our laboratories,[2] we now wish to report the total synthesis of a molecule with all the features of cephalothin in which the sulfur atom has been replaced by oxygen,[3] and in the accompanying article a similar molecule in which the sulfur has been replaced by methylene.[4]

Treatment of benzyl α-aminodiethylphosphonoacetate[2]

Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/ml

Compound	*Staphylococcus aureus* 2865	*Streptococcus pyogenes* 3124	*Klebsiella sp.* 2882	*Escherichia coli* 2884	*Shigella sp.* 2880	*Salmonella schottmuelleri* 2837
12a	<0.39	<0.39	6.25	6.25	6.25	6.25
Na cephalothin[a] (6(*R*),7(*R*))	<0.39	<0.39	3.12	6.25	3.12	3.12

[a] Racemic Na-cephalothin has approximately one-half the activity of 6(*R*),7(*R*)sodium cephalothin.[2]

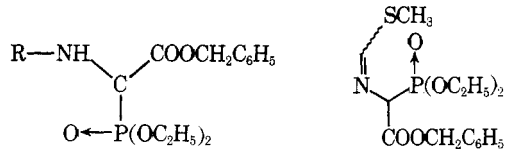
(**1**) with ethyl thionoformate in CCl_4 (addition at 0°, room temperature, overnight) gave benzyl α-thioformamidodiethylphosphonoacetate (**2**): ir (film) (μ) 3.1 (NH), 5.71 (C=O), 7.0 (C=S), 9.75 (P → O); nmr (CCl_4) δ 10.1 (NH), 9.4 (s, HC=S), 7.27 (s, C_6H_5), 6.02 (d, J = 21 Hz, CHP), 5.2 ($CH_2C_6H_5$), 4.07 (m, OCH_2CH_3), 1.25 (m, CH_3CH_2O). Treatment of **2** with anhydrous K_2CO_3 (1.1 equiv) and CH_3I (1.2 equiv) in acetone (room temperature, overnight, N_2 atmosphere) gave benzyl α-(*S*-methylthioimidato)diethylphosphonoacetate (**3**): ir (film) (μ) 5.72 (C=O), 6.25 (C=N), 9.75 (P—O); nmr (CCl_4) δ 8.47 (d, HC(S)=N), 7.35 (s, C_6H_5), 5.2 (s, $C_6H_5CH_2$), 4.66 (d, J = 22 Hz, CHP → O), 4.09 (m, CH_3CH_2O), 2.40 (s, CH_3S), 1.27 (m, CH_3CH_2O). When treated with azidoacetyl chloride (1.3 equiv) in CH_2Cl_2 followed by triethylamine (1.3 equiv) (N_2 atmosphere, room temperature, addition 10 min, stirring a further 10 min), **3** gave *trans*-1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-methylthio-2-azetidinone (**4**): ir (film) (μ) 4.75 (N_3), 5.6 (β-lactam), 5.72 (ester), 9.72 (P=O); nmr δ (CCl_4) 7.27 (s, C_6H_5), 5.16 (s, $C_6H_5CH_2$), 4.9-4.35 (complex m, β-lactam-H, and CHPO), 4.1 (m, OCH_2CH_3), 2.1 and 2.07 (2s, CH_3S, two isomers), 1.27 (m, CH_3CH_2-) in 42% overall yield from **1** (after silica gel chromatography using 50% EtOAc-C_6H_6 as eluent).

Treatment of **4** with 1.3 equiv of Cl_2 in CH_2Cl_2[5] gave 1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-chloro-2-azetidinone (**5**) as a mixture of cis and trans isomers: ir (film) (μ) 4.75, 5.6, 5.72, and 9.2; nmr ($CDCl_3$) δ 7.25 (s, C_6H_5), 6.2 (d, J = 4 Hz, $HCCl$), 6.04 (d, J = 4 Hz, $HCCl$), 5.77 (d, J = 1.5 Hz, $HCCl$), 5.6 (d, J = 1.5 Hz, HCCl), 5.23 (s, $C_6H_5CH_2$), 5.1-4.66 (m, NCH- and OPCH), 4.15 (m, CH_3CH_2O), 1.26 (m, CH_3CH_2O).

Chloroazetidinone **5** was dissolved in 1-hydroxy-3-acetoxy-2-propanone[6] (**6**) and treated with $AgBF_4$ (1.0 equiv) and Ag_2O (1.0 equiv) for 30 min at room temperature[7] to give 1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-(3′-acetoxy-2′-oxo)propyloxy-2-azetidinone (**7**): ir (film) (μ) 4.72 (N_3), 5.60 (β-lactam), 5.7 (ester), 5.85 (sh) (ketone) in 46% yield from **4**, as a mixture of cis and trans isomers in the ratio of 1:1. The reaction is believed to go through the ion **8** and the ratio of *cis*- and *trans*-**7** represents the ratio of the kinetic trapping of **8** by **6** from either face of **8**.

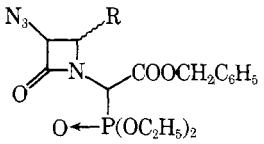
Ring closure of **7** with 1 equiv of NaH in DME (room temperature, 2 hr, N_2 atm) gave benzyl 7β-azido-1-oxadethiacephalosporanate (**9a**) (ir (film) (μ) 4.71, 5.58, 5.75, and 6.09 (C=C); nmr ($CDCl_3$) δ 7.44 (s, C_6H_5), 5.31 (s, $C_6H_5CH_2O$), 5.1 (AB q, CH_2OC=O), 5.07 (d, J = 3.5 Hz, C-6-H), 4.67 (d, J = 3.5 Hz, C-7-H), 4.94 (AB q, C-2-H), 2.05 (s, CH_3C=O)) and benzyl 7α-azido-1-oxadethiacephalosporanate (**9b**) (ir (film) (μ) 4.71, 5.58, 5.75, and 6.09; nmr ($CDCl_3$) δ 7.41 (s, C_6H_5), 5.34 (s, $C_6H_5CH_2O$), 5.03 (AB q, CH_2OC=O), 4.85 (d, J = 1 Hz, C-6-H), 4.5 (d, J = 1 Hz, C-7-H), 4.47 (s, C-2-H), 2.04 (s, CH_3C(H)=O)), in the ratio 1:1, separable by chromatography on silica gel (E. Merck, 10% EtOAc-C_6H_6) eluent in 28% yield from **7**.

Reduction of **9a** with 10% Pd/C (dioxane-water, 40 lb, 30 min) gave 7β-amino-1-oxadethiacephalosporanic acid (**10a**): ir (Nujol) (μ) 5.62 (β-lactam), 5.72 (sh) (ester), 6.25 (carboxylate). Acylation of **10a** with thienylacetyl chloride (acetone-H_2O, $NaHCO_3$ 2 equiv) gave, after acidification (pH 2) and extraction with EtOAc, 7β-(thienylacetamido)-1-oxadethiacephalosporanic acid (**11a**): ir (film) (μ) 5.60, 5.8, 6.0. This, when treated with 1 equiv of $NaHCO_3$ in acetone-H_2O gave sodium 1-oxacephalothin (**12a**):[3a] ir (Nujol) 5.60, 5.75, 6.0; nmr δ (D_2O, external TMS) 7.4 and 7.04 (m, thienyl H), 5.47 (d, J = 4 Hz, C-7-H), 5.17 (d, J = 4 Hz, C-6-H), 4.84 (d, CH_2OAc), 4.48 (s, C-2-H), 3.9

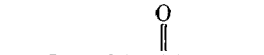


1, R = H
2, R = HC=S

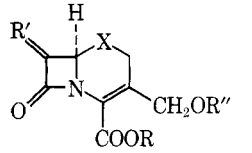
3

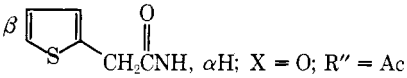
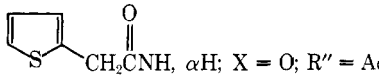
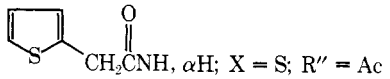
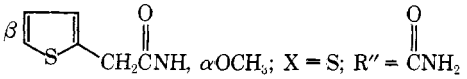


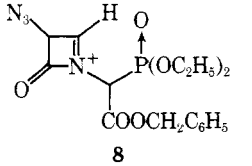
4, R = SCH_3(trans)
5, R = Cl(cis and trans)



7, R = $-OCH_2CCH_2OAc$
(cis and trans)



9a, R = $C_6H_5CH_2$; R′ = β-azido, αH; X = O; R″ = Ac
b, R = $C_6H_5CH_2$; R′ = α-azido, βH; X = O; R″ = Ac
10a, R = H; R′ = βNH_2, αH; X = O; R″ = Ac
11a, R = H; R′ = β  αH; X = O; R″ = Ac
12a, R = Na; R′ = β  αH; X = O; R″ = Ac
13, R = H; R′ = β  αH; X = S; R″ = Ac
14, R = H; R′ = β  αOCH₃; X = S; R″ = CNH_2



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(s, thienyl CH_2) 2.1 (s, $CH_3C{=}O$); $\lambda_{max}^{H_2O}$ 235 (ϵ 10,570), 255 (ϵ 6900 sh).

Table I compares the antimicrobial activity of compound **12a** with that of 6(*R*),7(*R*)-sodium cephalothin.

Acknowledgment. We are grateful to Dr. R. W. Ratcliffe for stimulating discussions during the course of this work. We thank Dr. E. H. Thiele for the *in vitro* results reported in this paper.

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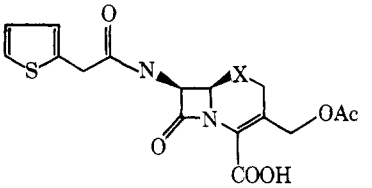
Received June 29, 1974

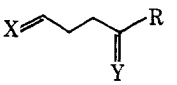
Total Synthesis of β-Lactam Antibiotics. VIII.[1a] Stereospecific Total Synthesis of (±)-1-Carbacephalothin[1b]

Sir:

As part of a program to devise convergent total syntheses of β-lactam analogs in our laboratories,[2] it was of interest to synthesize the nuclear analogs of the parent cephalosporins in which the sulfur atom is suitably substituted by simple isosteric groups. We now describe the stereospecific total synthesis of (±)-1-carbacephalothin[1b] (**1**), which embraces all the characteristic functionalities of cephalothin (**2**), except that the cephem sulfur has been replaced by methylene. Although partially substituted bicyclic analogs have been synthesized,[3] there appeared no report to date of the synthesis of the appropriately functionalized cephalosporin analog **1**. The crucial synthon **6** was synthesized as follows. 4-Pentenoyl chloride[4] reacted with diazomethane in ether (overnight, dark) to yield quantitatively 1-diazo-5-hexen-2-one (**3**): ir (μ) 4.72 (=N=N), 6.06 (C=O, C=C).[5] The diazoketone **3** decomposed in glacial acetic acid (1 hr, 60–70°) yielding the coupling product, 1-acetoxy-5-hexen-2-one (**4**) (90%): nmr 2.17 (s, CH_3), 4.67 (s, CH_2), 2.47 (m, CH_2CH_2), 4.82–6.17 (CH_2=CH); ir 5.70 (ester), 6.08 (C=C), 5.74 (C=O). Ketalization of **4** was accomplished smoothly (3 equiv of ethylene glycol, 10% *p*-TsOH by weight of ketone, benzene, 2 hr reflux) to give **5**

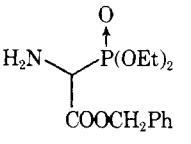


1, X = CH_2
2, X = S



3, X = CH_2; Y = O; R = CHN_2
4, X = CH_2; Y = O; R = CH_2OAc
5, X = CH_2; Y =  ; R = CH_2OAc
6, X = O; Y =  ; R = CH_2OAc

(90%): nmr 2.03 (s, CH_3), 1.7–2.15 (m, CH_2CH_2), 3.95 (s, CH_2CH_2), 4.0 (s, CH_2), 4.8–6.1 (m, CH_2=CH); ir 5.7 (ester) 6.06 (C=C). Oxidative scission of the double bond in **5** was achieved by cautious addition of 2 equiv of sodium metaperiodate to a heterogeneous mixture of olefin **5**, and 0.06 equiv of osmium tetroxide in ether and water (24–27°, 2.5 hr). The resulting aldehyde **6** was isolated in 60% yield after chromatography:[6] nmr 2.10 (s, CH_3), 2.04–2.6 (m, CH_2CH_2), 4.0 (s, CH_2CH_2), 4.03 (s, CH_2), 9.73 (t, CHO); ir 3.66 (CH of aldehyde), 5.7 (ester), 5.79 (C=O).



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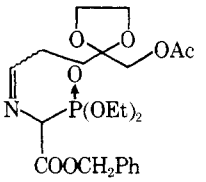

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The aldehyde **6** was condensed (ether, anhydrous magnesium sulfate, 1 hr, room temperature) with the amine **7**[2a] to give the unstable Schiff base, benzyl α-(5-acetoxy-4,4-ethylenedioxypentanaldimino)diethylphosphonoacetate (**8**): nmr 1.27 (t, CH_3), 2.08 (s, CH_3), 3.96 and 4.02 (s, CH_2CH_2 and CH_2), 4.5 (d, HCP, J = 20 Hz), 5.25 (s, CH_2), 7.38 (s, Ph), 7.82 (d, d, HC=N); ir 5.72 (esters), 6.0 (C=N). While other methods failed to produce even traces of β-lactam, an addition of an ethereal solution of the freshly prepared Schiff base **8** to a mixture of 1.5 equiv each of triethylamine and azidoacetyl chloride[7] at −78° in ether and warm-up of the reaction mixture to room temperature overnight resulted in the stereospecific cycloaddition to *cis*-1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-(3-ethylenedioxy-4-acetoxy)butyl-2-azetidinone (**9**): 30% after chromatography; nmr (100 MHz) 2.08 (s, CH_3), 4.70 (d, N_3CH, J = 5.5 Hz), 5.0 (d, HCP, J = 24 Hz), 5.22 (s, CH_2), 7.34 (s, Ph); ir 4.70 (N_3), 5.62 (β-lactam C=O), 5.69 (esters). Notably, this stereospecificity

Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/ml

Compound	*Staphylococcus aureus* 2865	*Streptococcus pyogenes* 3124	*Klebsiella sp.* 2882	*Escherichia coli* 2884	*Shigella sp.* 2880	*Salmonella schottmuelleri* 2837
15	1.56	<0.39	6.25	6.25	6.25	3.12
Na cephalothin[a] (6(*R*),7(*R*))	<0.39	<0.39	3.12	3.12	3.12	3.12

[a] Racemic Na cephalothin has approximately one-half the activity of 6(*R*),7(*R*)-sodium cephalothin.[2a]